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COGNITIVE ASSESSMENT WITH BICAMS AND COMPUTERIZED CANTAB TESTS DURING AND AFTER MULTIPLE SCLEROSIS RELAPSE

Summary of the Doctoral Thesis

Biomedical sciences, medicine (06 B)

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VILNIAUS UNIVERSITETAS

NATAŠA GIEDRAITIENĖ

KOGNITYVINIŲ FUNKCIJŲ VERTINIMAS IŠSĖTINĖS SKLEROZĖS PAŪMĖJIMO IR ATSISTATYMO LAIKOTARPIAIS REMIANTIS *BICAMS* IR KOMPIUTERIZUOTŲ *CANTAB* TESTŲ REZULTATAIS

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ABBREVIATION

BICAMS - Brief International Cognitive Assessment for Multiple Sclerosis

BVMT-R - Brief Visuospatial Memory Test-Revised

BVMT-R-R – BVMT-R result during the relapse

BVMT-R(1-R) – the difference of BVMT-R results between the 1st month and relapse

BVMT-R(3-R) – the difference of BVMT-R results between the 3rd month and relapse

CANTABeclipse - Cambridge Neuropsychological Test Automated Battery

CVLT-II - California verbal learning test, second edition

CVLT-II-R – CVLT-II reslt during the relapse

CVLT-II(1-R) – the difference of CVLT-II results between the 1st month and relapse

CVLT-II(3-R) – the difference of CVLT-II results between the 3rd month and relapse

EDSS - Expanded Disability Status Scale

EDSS-R – EDSS score during relapse

EDSS-S – EDSS score during remission

EDSS(S-R) – deterioration in EDSS score

IMG-R – initiation of immunomodulatory therapy during relapse

MS – multiple sclerosis

MSr – relapsing multiple sclerosis patients

MSr1 – relapsing MS patients during relapse

MSr2 – relapsing MS patients during 1st month after relapse

MSr3 – relapsing MS patients during 3rd month after relapse

MSs – stable multiple sclerosis patients

CG – control group

CIS – clinically isolated syndrome

MxA - Myxovirus resistance gene

OTS – One touch stockings of Cambridge

OTSMechco – Mean choice to correct of OTS

OTSMelaco – Mean latency to correct of OTS

OTSMelach – Mean latency to first choice of OTS

OTSProfi – Problems solved on first choice of OTS

OTSMechco1/2/3/4/5/6 – Mean choice to correct of 1, 2, 3, 4, 5 and 6 moves of OTS

OTSProfi1/2/3/4/5/6 – Problems solved on first choice of 1, 2, 3, 4, 5 and 6 moves of OTS

PAL - Paired Associates Learning

PALfitme - First trial memory score of PAL

PALMeer - Mean errors to success of PAL

PALMetr - Mean trials to success of PAL

PALStac - Stages completed of PAL

PALStfir - Stages completed on first trial of PAL

PALToer - Total errors of PAL

PALToer1/2/3/6/8 - Total errors at 1, 2, 3, 6 and 8 pattern stages of PAL

PALTotr - Total trials of PAL

PALTotr1/2/3/6/8 - Total trials at 1, 2, 3, 6 and 8 pattern stages of PAL

RRMS – relapsing remitting multiple sclerosis

RTI – Reaction time

RTIFichomot – Five-choice movement time of RTI

RTIFichoret – Five-choice reaction time of RTI

RTISacsco – Simple accuracy score of RTI

RTISimot – Simple movement time of RTI

RTISiret – Simple reaction time of RTI

R^2- coefficient of determination

SDMT - Symbol Digit Modalities Test

SDMT-P – SDMT result during relapse

SDMT(1-R) – the difference of SDMT results between the 1st month and relapse

SDMT(3-R) – the difference of SDMT results between the 3rd month and relapse

SPMS - secondary progressive multiple sclerosis

SWM - Spatial Working Memory

SWMbeer - Between errors of SWM

SWMbeer4/6/8 - Between errors for 4, 6 and 8 boxes of SWM

SWMstrat – Strategy of SWM of SWM

SWMtoer – Total errors of SWM

SWMtoer4/6/8 - Total errors for 4, 6 and 8 boxes of SWM

1 INTRODUCTION

Multiple sclerosis (MS) is an immune-mediated demyelinating disease of the central nervous system which affects young and middle-aged adults and most commonly presents with a relapsing-remitting course. MS can cause a wide range of symptoms, including decline of cognitive abilities. Cognitive impairment (CI) in MS patients substantially impacts the lives of the patients and their families. Half to three-quarters of people with MS are unemployed within 10 years of diagnosis. CI is the leading predictor of occupational disability, while physical disability, age, sex, and education account for less than 15% of the likelihood of being employed.

Studies on the prevalence of CI in MS patients show that CI occurs in up to 70% of MS patients. It involves all the subtypes of MS and often is found in early stages of MS, even in case of clinically and radiologically isolated syndromes. Often the degree of the impairment can be mild and patients may not be fully aware of it. Despite a high prevalence of CI in MS patients, still the cognitive assessment and follow-up of cognitive status are not performed regulary.

In recent decades the assessment of cognitive decline related to MS has received increasing attention. Many different neuropsychological batteries have been proposed. Among the most frequently used instruments is the Brief Repeatable Battery of Neuropsychological tests (BRB-N). Another popular assessment instrument is the Minimal Assessment of Cognitive Function in MS (MACFIMS). While both batteries are known to be highly specific for the evaluation of CI in MS patients, their implementation in everyday clinical practice remains limited due to their high time demand and the need for surveillance and interpretation by proficient neuropsychologists. Due to these limitations, there have been considerable efforts made over the past decade to create a simpler but specialized neuropsychological instrument for the assessment of CI in MS patients; the result is the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) battery. The BICAMS battery is very short and highly sensitive. It is easily administered (the time needed for full assessment is 15 minutes). BICAMS does not require any special equipment or training and the battery may be conveniently used in everyday clinical practice. It is convenient for neurologists dealing with a small number of MS patients and MS practices with very few staff neurologists, without specialized neuropsychological training. Regardless of BICAMS battery simplicity, the assessment with BICAMS is not readily available in most countries, although it is widely recognized that the assessment and follow-up of cognitive status, as well as treatment (in case of

deterioration), should be as much a priority as is the evaluation and treatment of physical disability in MS patients.

Studying cognition during MS relapses is another hotly debated issue nowadays. Usually MS relapses are diagnosed via neurological examination quantified with the Expanded Disability Status Scale (EDSS). EDSS is quite sensitive in assessing the ability to move and remains the gold-standart measure for assessing the level of disability. However, the EDSS only cursorily assesses the alteration in cognitive functions. It is thought that cognition also is affected during MS relapse and so-called "cognitive-relapses" are hypothesized to occur and may be more common than is currently appreciated due to the lack of appropriate measurement tools. Most likely due to a luck of research there are no widely accepted guidelines for treating MS patients who have cognitive complaints and active post-contrast magnetic resonance imaging (MRI) lesions, but minimal sensory and (or) motor deficit. So from the clinical and scientific point it is useful to examine the neurocognitive status along with other aspects of neurological disability during MS relapse and to enhance the understanding of the clinically meaningful changes on cognition outcomes that may occur as a result of neurological worsening or response to treatment.

1.1 THE AIM OF THE STUDY

To assess the cognitive functions with the Lithuanian version of Brief International Cognitive Assessment for MS (BICAMS) and computerized tests (CANTABeclipse 3.0.0) in relapsing MS patients during MS relapse and 3-month follow-up period and to compare the neurocognitive results of relapsing MS patients with the stable MS patients and healthy controls results.

1.2 THE OBJECTIVES OF THE STUDY

1. To assess the cognitive functions with the Brief International Cognitive Assessment for MS and computerized CANTABeclipse tests in MS patients during the relapse and to compare the neurocognitive results in relapsing and stable MS patients.
2. To compare the cognitive functions with Brief International Cognitive Assessment and CANTABeclipse tests in both relapsing and stable MS patients with those of healthy controls.
3. To assess the neurocognitive outcomes over a 3 month follow-up period after MS relapse.

4. To determine the factors that have the impact on the neurocognitive changes after MS relapse.
5. To analyse the diagnostic value of computerized tests in assessment of neurocognitive status during MS relapse.

1.3 SIGNIFICANCE AND SCIENTIFIC NOVELTY OF THE STUDY

Relapsing MS patients were assessed completely – not only physical disability usually estimated in routine clinical practice, but also cognitive disability was assessed. The Brief International Cognitive Assessment for MS was translated into Lithuanian and Lithuanian version of BICAMS with the computerized CANTABeclipse tests were used for the assessment of cognitive status during MS relapse and recovery. There were no conducted in Lithuania and in the world such comprehensive studies evaluating the cognition during MS relapse and assessing different factors that could have the impact on the cognition and predict its recovery. In our opinion, the obtained results will add to the knowledge of the world's scientists on the understanding of the clinically meaningful changes on cognition outcomes and will provide an opportunity for the clinicians to assess cognition quickly and in the case of cognitive deterioration to recognize the „cognitive-relapse" efficiently.

2 MATERIALS AND METHODS OF THE STUDY

The clinical research study was initiated at the Neurology and Neurosurgery Clinic, Faculty of Medicine at Vilnius University, Vilnius University Hospital Santariskiu Clinics from 2012 to 2016. The study protocol was approved by the Lithuanian Bioethics Committee (No. 158200-13-644-191) and written informed consent was obtained from each study participant.

2.1 Selection and grouping of participants

120 subjects were enrolled in the study: 60 relapsing (MSr), 30 stable (MSr) MS patients and 30 healthy persons (CG) matched for age, gender and years of education. Stable MS patients had no MS relapse at least 3 months before the enrollment.

Inclusion criteria for MS patients were:

- Subjects older than 18 years of age;

- MS diagnosis based on the revised McDonald criteria (2010 Revisions);
- Relapsing remitting, secondary progressive MS or clinically isolated syndrome;
- No evidence of any neurological or psychiatric disorder other than MS, not limited to major head trauma, seizures, or systemic medical diseases, that are likely to affect cognitive functioning;
- Patients had received no prior any cognition-enhancing medication (e.g., antidepressants, neuroleptics, and anticholinergic drugs) within 1 month prior to enrolment;
- Stable MS patients had no MS relapse at least 3 month prior the assessment;
- All MS patients were steroids- and (or) plasmapheresis-free for at least 3 month preceding the enrolment;
- The patients were proficient in the Lithuanian language.

Exclusion criteria for MS patients were any findings controverted to the inclusion criteria.

The CG included healthy persons with no history of any cognitive dysfunction, with sight and hearing sufficient for compliance with the study assessment and proficient in the Lithuanian language.

2.2 Clinical and neurological assessment

MS was diagnosed at Vilnius University Hospital Santariskiu Clinics, Department of Neurology according to the revised McDonald 2010 criteria. MS relapses were recognised in the cases of worsening or new neurological symptoms appearance that lasted for at least 24 hours and were diagnosed using the Expanded Disability Status Scale (EDSS). The clinical pattern and course of MS – relapsing-remitting, secondary progressive or clinically isolated syndrome, were defined according to the Lublin and Reingold the clinical course difinings, 2013 revisions.

2.3 Immunological assessment of interferon-beta

In patients who were treated with interferon-beta for at least 1.5 year the biological activity of interferon-beta was assessed by measuring the marker of interferon-beta activity – myxovirus resistance protein A (MxA). Biological responders, poor biological responders, and biological non-responders were defined based on the absolute values of their MxA expression/induction indicators regarding 2 cut-off values established before the study. Biological responders were defined as the patients whose MxA expression values were above both threshold levels. In case

only 1 threshold was reached, a patient was assigned to the group of poor biological responder. If neither of the 2 thresholds was reached, a patient was defined as a biological non-responder. MxA mRNA expression cut-off of <0.586 before interferon-beta injection and MxA mRNA expression cut-off of <3.84 after INF-b injection were considered as negative.

2.4 Neuropsychological assessment with BICAMS and CANTABeclipse batteries

All subject were assessed by the same person and in the same room. Relapsing MS group was examined during the relapse, 1st and 3rd months after relapse. Assessment during relapse was made before the relapse treatment and the relapse was treated according to the standart clinical practice – steroids and (or) plasmapheresis was (were) given for the treatment. Single assessement was made for stable MS patients and control group.

2.4.1 The cognitive assessment with BICAMS

All subject were examined with BICAMS in the same sequence:

1. The Symbol Digit Modalities Test (SDMT);
2. The Brief Visuospatial Memory Test Revised (BVMT-R), first 3 recall trials;
3. The California verbal learning test, second edition (CVLT-II), first 5 trials.

SDMT is used for evaluation of information processing speed in MS patients. It presents a sequence of 9 symbols. Any 1 of these symbols is paired with a single digit in the upper part of the page. The working area of the page contains the pseudo-randomized sequence of these symbols. Tested participants respond by saying the digit, which is paired with the appropriate symbol at the top of the page, as quickly as possible. The indicator of performance is the total number of correct pairings in 90 seconds.

BVMT-R is a test to evaluate visuospatial memory and learning. A group of 6 simple figures are shown to the participants for 10 seconds. After the presentation of the visual stimulus figures, participants try to draw the correct figures using a pencil on a sheet of paper. The test time is not limited. Each figure reproduced by a participant may be scored 0, 1, or 2 based on the scoring criteria for accuracy and location. The indicator of performance is total recall score in all 3 trials.

CVLT-II is a tool for measuring verbal memory and learning. The initial 5 trials were used to evaluate the ability of a participant to learn a 16-word list. The 16-word list is read aloud by the investigator. After the full list has been read, the participants are asked to repeat as many words as

they can remember. The entire list of words is read aloud by the investigator during each trial. The indicator of performance is the total number of words recalled during all 5 learning trials. Delayed CVLT-II recall of 16 words was assessed again after CANTAB performance.

2.4.2 The cognitive assessment with CANTABeclipse

From 22 possible computerized CANTABeclipse tests 4 tests were included in the battery:

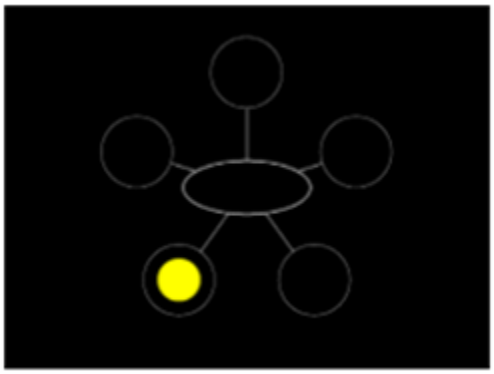
- Reaction time (RTI) – measures speed of response and movement in single and 5-choice paradigms,
- One touch stockings of Cambridge (OTS) – assesses spatial planning,
- Paired Associates Learning (PAL) – assesses episodic memory and learning,
- Spatial Working Memory (SWM) – assesses working memory and strategy use.

Reaction time (RTI) – measures the subject's speed of response to a visual target. The task is divided into the five stages, each successive stage having increasingly complex response requirements. In the first stage, the subject simply has to touch the screen when a yellow spot appears in the centre of the screen. Once the subject has achieved 5 out of 6 correct, or completed a maximum of 18 attempts, the second stage, which is the choice reaction task, is introduced. In the second stage, the yellow spot may now appear in any one of five locations. Again, the subject is trained to a criterion of 5 out of 6 correct, with a maximum of 40 attempts. In the third stage, the subject is required to hold down the press pad button until the yellow spot appears in the centre of the screen and in the fourth stage, the subject is required to hold down the press pad button and then must touch the screen where the spot appears. In the fifth and final stage, the choice reaction task is again introduced, and by this stage the subject has been trained to hold down the press pad button until the spot appears, then release the press pad button and touch the position on the screen where the spot was presented.

The outcome measures for RTI test are:

- Five-choice movement time (RTIFichomot),
- Five-choice reaction time (RTIFichoret),
- Simple accuracy score (RTISacsco),
- Simple movement time (RTISimot),
- Simple reaction time (RTISiret).

Figure 1. **The example of Reaction time test**

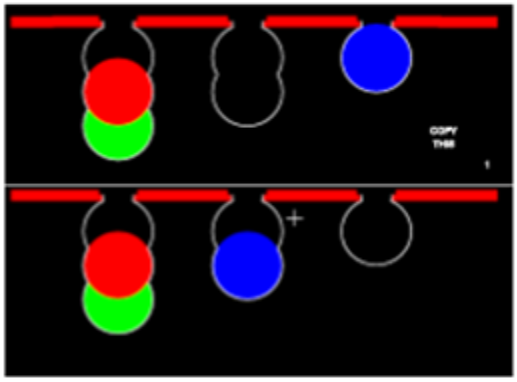


One touch stockings of Cambridge (OTS) test gives the measure of frontal lobe function. In OTS task the displays are presented in such a way that they can easily be perceived as stacks of coloured balls held in stockings or socks suspended from a beam. The test administrator first demonstrates to the subject how to use the balls in the lower display to copy the pattern shown in the upper display. The balls may be moved one at a time by touching the required ball, then touching the position to which it should be moved. The subject is shown one demonstration problem, then must solve three further problems. These problems increase in complexity, from one move to four moves. If the subject makes too many moves in attempting to solve these problems, the computer presents the ideal solution to the subject. Next the subject is shown more problems, and must work out how many moves the solutions require in their head, then touch the appropriate box at the bottom of the screen to indicate the number of moves required (Figure 2).

The outcome measures for OTS test are:

- Mean choice to correct: total (OTSMechco) and of different moves (from 1 up to 6: OTSMechco1, OTSMechco2, OTSMechco3, OTSMechco4, OTSMechco5 and OTSMechco6),
- Mean latency to correct (OTSMelaco),
- Mean latency to first choice (OTSMelach),
- Problems solved on first choice: total (OTSProfi) and of different moves (from 1 up to 6: OTSProfi1, OTSProfi2, OTSProfi3, OTSProfi4, OTSProfi5 and OTSProfi6).

Figure 2. **The example of One touch stockings of Cambridge test**

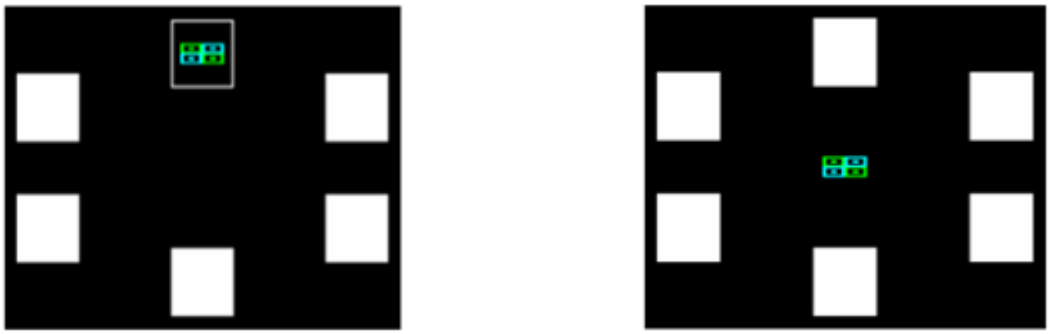


Paired Associates Learning (PAL) - assesses visual memory, new learning and is primarily sensitive to changes in medial temporal lobe functioning. In PAL task boxes are displayed on the screen and are opened in a randomised order. One or more of them will contain a pattern. The patterns shown in the boxes are then displayed in the middle of the screen, one at a time, and the subject must touch the box where the pattern was originally located. Each stage may have up to 10 trials in total (the first presentation of all the shapes, then up to 9 repeat presentations). If the subject makes an error, the patterns are represented to remind the subject of their locations. When the subject gets all the locations correct, they proceed to the next stage. If the subject cannot complete a stage correctly, the test terminates.

The outcome measures for PAL test are:

- First trial memory score (PALfitme),
- Mean errors to success (PALMeer),
- Mean trials to success (PALMetr),
- Stages completed (PALStac),
- Stages completed on first trial (PALStfir),
- Total errors (PALToer) and total errors at different pattern stages (1, 2, 3, 6 and 8 figures: PALToer1, PALToer2, PALToer3, PALToer6 and PALToer8),
- Total trials (PALTotr) and total trials at different pattern stages (1, 2, 3, 6 and 8 figures: PALTotr1, PALTotr2, PALTotr3, PALTotr6 and PALTotr8).

Picture 3. **The example of Paired Associates Learning test**

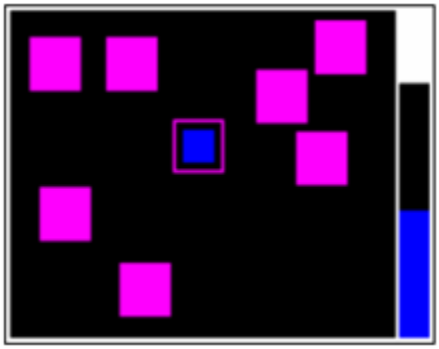


Spatial Working Memory (SWM) - is a test of the subject's ability to retain spatial information and to manipulate remembered items in working memory. This test is a sensitive measure of frontal lobe and 'executive' dysfunction. SWM test begins with a number of coloured squares (boxes) being shown on the screen. The aim of this test is that, by process of elimination, the subject should find one blue 'token' in each of a number of boxes and use them to fill up an empty column on the right hand side of the screen („home"). The number of boxes is gradually increased from three to eight boxes. The colour and position of the boxes used are changed from trial to trial to discourage the use of stereotyped search strategies. Touching any box in which a blue token has already been found is an error. Performance at the harder levels of this task is enhanced by the use of a heuristic search strategy.

The outcome measures for SWM test are:

- SWM Between errors: total (SWMbeer) and for 4, 6 and 8 boxes (SWMbeer4, SWMbeer6 and SWMbeer8),
- SWM Strategy (SWMstra),
- SWM Total errors (SWMtoer) and total errors for 4, 6 or 8 boxes (SWMtoer4, SWMtoer6 and SWMtoer8).

Picture 4. **The example of Spatial Working Memory test**



2.5 Methods of statistical analysis

Data were analysed using statistical software package SPSS (version 20.0 for Windows). Descriptive statistic is presented as mean (m) and standard deviation (±SD). Student's t-test was used to compare mean of the same characteristic in two groups, when characteristic distribution was normal. Categorical variables were analysed using Chi-square of exact Fisher's test. To check the distribution of normality of quantitative variables Kolmogorov-Smirnov compatibility criteria was used.

For the primary hypothesis analysis of variance (ANOVA) model was used whereby the MS patients (relapsing and stable) and CG between-group factor was coupled and for the significance within groups post-hoc Bonferroni (for equal variances, Levene test >0.05) or Tamhane (for unequal variances, Levene test <0.05) test was used. GLM Repeated Measures were used when measuring the data of relapsing MS patients at different time points (relapse, first and third months after relapse). Logistic regression analysis was used to assess the association between the changes of neurocognitive data after the relapse and various cognitive and non-cognitive factors.

Significance level is fixed and equals 0.05.

3 RESULTS

3.1 General characteristics of study subjects

A total of 120 subjects were included in the study: 90 patients with clinically definite MS (60 relapsing (MSr) and 30 stable (MSs)) and 30 healthy control subjects (CG). All groups were

well matched on the demographic characteristics (Table 1), also MSr and MSs groups - on the disease characteristics (Table 2).

Table 1. **Demographic characteristics in participant groups.**

	MSr patients	**MSs patients**	**CG**	**Test**
Number of subjects, N	60	30	30	–
Gender Women/Men, N	21/39	13/17	12/18	$\chi 2 = 0.635$ p=0.728
Age (years) Mean±SD	38.43±9.6 (18-61)	37.47±10.3 (22-59)	37.63±9.5 (24-56)	ANOVA F= 0.13 p=0.883
Education (years) Mean±SD	14.80±2.3	14.88±2.8	15.42±1.8	ANOVA F=0.877 p=0.419

MSr – relapsing MS patients, MSs – stable MS patients, CG – control group

Table 2. **Clinical characteristics in MS patients.**

	MSr patients	**MSs patients**	**Test**
Number of subjects, N	60	30	-
Duration of the disease (years) Mean±SD	8.94±7.2	8.30±7.5	p= 0.697
EDSS (in MSr during the 3rd mth before the relapse)	3.59±1.3 (N49)	3.25±1.19	p=0.243
EDSS (in MSr during the 3rd mth after the relapse)	3.78±1.26	3.25±1.19	p=0.061
The mean number of exacerbations	4.82±3.3	3.83±2.4	p=0.108
The period of remission (mth) CI [lower-upper limit]	23.22±23.80 [17.07-29.37]	30.2±29.18 [19.31-41.10]	p=0.228
The duration of immuno-modulatory therapy (years) CI [lower-upper limit]	3.40±3.42 [2.49-4.31]	3.33±3.41 [2.06-4.61]	p=0.931

MSr – relapsing MS patients, MSs – stable MS patients, EDSS - Expanded Disability Status Scale, CI – confidence interval

56 (93.3 %) relapsing MS patients had relapsing remitting MS (RRMS), 2 (3.3 %) patients - secondary progressive MS (SPMS) and 2 (3.3 %) patients - clinically isolated syndrome (CIS). Stable MS patients were similarly distributed according to the course of the disease: 27 (90.0 %) had RRMS and 3 (10.0 %) patients – CIS ($\chi 2 = 2.62$, p=0.269).

The duration of the relapse in MSr patients ranged from 4 up to 180 days (mean±SD 47.77±43.38 days). The longer duration of the relapse was significantly associated with the higher

age and lower education (accordingly r=0.296, p=0.022 and r=–0.260, p=0.045). Also the longer duration of the relapse was associated with more severe deterioration in mean EDSS score assessed during relapse and lower mean EDSS decrease after the relapse treatment (accordingly r=0.287, p=0.045 ir r= -0.320, p=0.013).

In MSr and MSs patients the annualized relapse rate was calculated: the annualized relapse rate = number of relapses / duration of the disease. The median of the annualized relapse rate in MSr patients (IQR) was 0.67 (0.40-0.92), in MSs patients – 0.54 (0.31-1.00). MSr and MSs patients well matched on the annualized relapse rate (p=0.438).

29 (48.3 %) MSr patients were treated with intravenous methylprednisolone, 6 (10.0 %) patients – with plasma exchange and 25 (41.7 %) – with methylprednisolone and plasma exchange. Most of the patients - 43 (71.6 %), were treated with methylprednisolone over a period of 3 days, 6 patients (10.0 %) – of 4 days, 4 patients (6.7 %) – of 5 days and 1 patient (1,7 %) – of 6 days.

EDSS in patients treated with methylprednisolone during the relapse was significantly lower by 0.92±0.31 point than treated with methylprednisolone and plasma exchange (ANOVA F=4.50, p=0.012). The EDSS score decreased significantly more in patients treated with higher dose of steroids: in patients who were treated with 5 grams of methylprednisolone the EDSS was decreased by 1.75±0.26 point and in patients treated with 3 or 4 grams - by 0.85±0.08 and 0.67±0.21 points accordingly (ANOVA F=4.45, p=0.008).

EDSS score during and after MS relapse was assessed in interferon-beta biological responders (11 patients, 18.3 %), poor biological responders (10 patients, 16.7 %) and non-responders (2 patients, 3.3 %). Poor biological responders and non-responders were analysed together. No significant differences in EDSS score were observed in biological responders and poor-biological / non-responders during and after MS relapse (p>0.05).

3.1.The assessment of cognitive functions with BICAMS and CANTAB tests

A total of 240 testings were performed with BICAMS and CANTAB batteries: relapsing MS patients (N–60) were tested three times (during relapse, 1st and 3rd months after relapse), stable MS patients (N-30) and CG (N-30) were tested once. The BICAMS tests took approximately 15 min. The whole CANTAB test lasted approximately 46.26±13.19 min. (from 22.77 up to 102.63 min.): in MS patients (relapsing and stable) the testing lasted significantly longer than in CG

(accordingly 51.02±14.24, 45.08±11.20 and 37.90±7.46), however, there were no significant differences between testing time in MSr and MSs patients (ANOVA F=11.89, p<0.001).

3.1.1. The assessment with BICAMS tests

The mean scores of all three BICAMS tests (SDMT, BVMT-R and CVLT-II) and CVLT-II delayed recall were compared in MSr, MSs and CG and they were significantly lower in MS patients (also relapsing and stable), than in CG. The most affected cognitive domain ir relapsing MS patients was verbal learning – the mean CVLT-II score was by 14.95 points lower in relapsing MS patients than in CG. Less affected were information processing speed and visuospatial learning and memory: the mean scores in relapsing MS patients were accordingly by 13.65 and 6.46 points lower than in CG. The mean SDMT score was significantly lower by 6.42 points in relapsing MS patients, than in stable MS patients, however, no significant differences were found between mean scores of BVMT-R, CVLT-II and CVLT-II delayed recall in relapsing and stable MS patients (Table 3).

Table 3. **The mean scores of BICAMS in MS patients and control group**

Test	**MSr group (N-60)**	**MSs group (N-30)**	**CG (N-30)**	**ANOVA**	**Post-hoc**
SDMT	40.18±11.42	46.60±11.54	53.83±8.91	F=16.07; p<0.001	CG>MSs>MSr*
BVMT-R (0-36)	22.57±6.07	25.23±5.66	29.03±4.22	F=13.63; p<0.001	CG>MSs,MSr MSs=MSr*
CVLT-II (0-80)	52.02±9.61	54.80±9.40	66.97±4.68	F=30.99; p<0.001	CG>MSs,MSr MSs=MSr**
CVLT-II delayed recall (0-16)	12.23±2.66	12.80±3.12	15.40±0.72	F=16.86; p<0.001	CG>MSs, MSr MSs=MSr**

BICAMS - Brief International Cognitive Assessment for MS, MSr – relapsing MS patients, MSs – stable MS patients, CG – control group, SDMT - Symbol Digit Modalities Test, BVMT-R - Brief Visuospatial Memory Test-Revised, CVLT-II - California verbal learning test, II ed.

* Bonferroni test was used for post-hoc analysis

** Tamhane test was used for post-hoc analysis

After comparing the mean results of BICAMS in MS patients and CG, the mean scores during relapse, 1st and 3rd months after relapse were compared in relapsing MS patients. Mean scores of all three BICAMS tests were significantly higher during the 1st month after relapse than during the relapse: the mean score of SDMT test was higher by 6.02±6.14 points, BVMT-R – by

3.73±4.93 points, CVLT-II – by 6.43±6.00 points and CVLT-II delayed recall - by 1.48±1.94 point during the 1st month after relapse than during the relapse. The mean score of CVLT-II test was significantly higher by 2.12 points during the 3rd month after relapse than during the 1st, however, there were no significant differences between SDMT and BVMT-R tests results assessed during the 3rd and 1st months in relapsing MS patients (Table 4).

Table 4. **The mean scores of BICAMS tests during and after MS relapse in relapsing patients**

Test	**MSr1 group (N-60)**	**MSr2 group (N-60)**	**MSr3 group (N-60)**	**ANOVA**	**Post hoc**
SDMT	40.18±11.42	46.20±12.28	46.62±10.96	F=43.08; p<0.001*	MSr1<MSr2,MSr3 MSr2=MSr3
BVMT-R (0-36)	22.57±6.07	26.30±4.56	26.93±4.62	F=34.73; p<0.001*	MSr1<MSr2,MSr3 MSr2=MSr3
CVLT-II (0-80)	52.02±9.61	58.45±8.36	60.57±9.59	F=65.87; p<0.001	MSr1<MSr2<MSr3
CVLT-II delayed recall (0-16)	12.23±2.66	13.72±2.22	13.98±2.04	F=33.84; p<0.001*	MSr1<MSr2,MSr3 MSr2=MSr3

MSr1 – relapsing MS patients during relapse, MSr2 – relapsing MS patients during the 1st mth after relapse, MSr3 – relapsing MS patients during the 3rd mth after relapse, SDMT - Symbol Digit Modalities Test, BVMT-R - Brief Visuospatial Memory Test-Revised, CVLT-II - California verbal learning test, II ed.
*- Greenhouse-Geisser criterion was used.

To assess the impact of various demographic, clinical and imunological factors on the cognition after relapse new measures were obtained - the difference between the BICAMS test results during the 1st or 3rd month and relapse was calculated. The collected new measures were SDMT(1-R), SDMT(3-R), BVMT-R(1-R), BVMT-R(3-R), CVLT-II(1-R) and CVLT-II(3-R). Logistic regression was used to assess and to explain the relationship between new cognitive parameter and various independent cognitive and non-cognitive factors (demographic, clinical and immunological): age, gender, education, working status, the course of the disease, the duration of the disease, EDSS score before the relapse, during and after relapse, the deterioration in EDSS score before the relapse and the improvement after the relapse, the duration of the relapse, the treatment of the relapse (methylprednisolone / plasmapheresis / rehabilitation), time to the initiation of immunomodulatory treatment after the relapse, the duration of the immunomodulatory therapy, biological activity of the interferon-beta, relapse rate, the duration of the remission before

the relapse. Stepwise linear regression was used and in the models independent variables were included with statistical significance <0.05 (Table 5).

Table 5. **Regression models predicting the cognitive changes after MS relapse**

Dependent variable	**Regression models**	**R^2**	**P (R^2; coefficients)**
SDMT(3-R)	11.72 – 0.29 x SDMT-R + 0.61 x education – 0.12 x age	0.243	<0.001; <0.05
SDMT(3-R)	7.06 – 2.98 x EDSS(S-R) – 0.12 x SDMT-R	0.311	<0.001; <0.05
SDMT(3-R)	5.61 + 3.09 x EDSS-R – 2.79 x EDSS-S – 0.12 x SDMT-R	0.306	<0.001; <0.05
SDMT(3-R)	18.27 – 4.12 x IMG-R – 0.16 x SDMT-R	0.153	=0.042; <0.05
BVMT-R(1-R)	23.77– 0.52 x BVMT-R-R – 3.1 x gender – 2.2 x rehabilitation	0.563	<0.001; <0.05
BVMT-R(3-R)	20.98 – 0.54 x BVMT-R-R – 3.98 x methylprednisolone	0.483	<0.001; <0.05
BVMT-R(3-R)	24.87 – 0.67 x BVMT-R-R – 3.01 x biological activity of IFN-beta	0.755	<0.001; <0.05
CVLT-II(1-R)	15.49 – 0.27 x CVLT-II-R + 1.99 x gender	0.286	<0.001; <0.05
CVLT-II(3-R)	30.40 -0.37 x CVLT-II -R – 0.46 x duration of the relapse	0.292	<0.001; <0.05

R^2- coefficient of determination, SDMT(3-R) – the difference of SDMT results between 3rd month and relapse, SDMT-R – SDMT result during relapse, EDSS(S-R) – deterioration in EDSS score (from remission up to the relapse), EDSS-R – EDSS score during relapse, EDSS-S – EDSS score during remission (3rd month before the relapse), IMG-R – initiation of immunomodulatory therapy during the 1st month after relapse, BVMT-R(1-R) – the difference of BVMT-R result between 1st month and relapse, BVMT-R-R - BVMT-R result during relapse, BVMT-R(3-R) – the difference of BVMT-R result between 3rd month and relapse, CVLT-II(1-R) – the difference of CVLT-II result between 1st month and relapse, CVLT-II-R – CVLT-II result during relapse, CVLT-II(3-R) – the difference of CVLT-II result between 3rd month and relapse.

In all models one of the most important variable was the result of the BICAMS test during the relapse: SDMT-R, BVMT-R-R or CVLT-II-R. The result of BVMT-R significantly improved in men, while the result of CVLT-II – in women. The gender had no significant impact on the SDMT test result, however, it was the only test which result was impacted by the EDSS score during the relapse and remission or mean EDSS deterioration (the difference in EDSS score from remission and relapse). Also relapse treatment with methylprednisolone, biologically active interferon-beta and rehabilitation after relapse had the positive impact on the improvement of BVMT-R result and

the shorter duration of the relapse (or early treatment of relapse) had the positive impact on the CVLT-II result.

3.1.2 The assessment with CANTABeclipse tests

3.1.2.1 The results of Reaction time test

The results of RTI test were compared in relapsing, stable MS patients and healthy controls. The mean scores of simple movement time (RTISimot), simple reaction time (RTISiret), five-choice movement time (RTIFichomot) and five-choice reaction time (RTIFichoret) were significantly higher in MS patients than in CG ($p<0.05$), while in relapsing and stable MS patients there were no significant differences between mean scores of above-mentioned values ($p>0.05$). The mean duration of RTI test was lower in CG than in MSs group, however, the difference was not significant, while MSr patients performed the RTI test significantly longer than MSs and CG ($p=0.001$). And only simple accuracy score of RTI test didn‘t differ between all three groups ($p>0.05$) (Table 6).

Table 6. **The mean scores of RTI test in MS patients and control group**

Test	**MSr group (N-60)**	**MSs group (N-30)**	**CG (N-30)**	**ANOVA**	**Post-hoc**
RTI duration (sec.)	355.00± 79.47	321.03± 26.70	308.43± 32.76	F=7.03; p=0.001	CG,MSs<MSr, CG=MSs**
RTIFichomot (msec.)	569.30± 182.95	563.00± 316.74	359.75± 76.25	F=11.22; p<0.001	CG<MSs,MSr, MSs=MSr**
RTIFichoret (msec.)	416.73± 99.74	377.73± 68.67	332.10± 47.85	F=10.80; p<0.001	CG<MSs,MSr MSs=MSr**
RTISacsco	8.75± 0.65	8.87± 0.78	8.50± 0.63	F=2.32; p=0.103	-
RTISimot (msec.)	631.11± 188.40	625.55± 288.40	459.99± 194.24	F=6.74; p=0.002	CG<MSs,MSr MSs=MSr*
RTISiret (msec.)	392.95± 95.46	368.29± 88.72	305.98± 43.06	F=10.82; p<0.001	CG<MSs,MSr MSs=MSr**

MSr – relapsing MS patients, MSs – stable MS patients, CG – control group, RTI – reaction time, RTIFichomot - five-choice movement time of RTI, RTIFichoret – five-choice reaction time of RTI, RTISacsco – simple accuracy score of RTI, RTISimot – simple movement time of RTI, RTISiret – simple reaction time of RTI.

* Bonferroni test was used for post-hoc analysis

** Tamhane test was used for post-hoc analysis

The mean scores of RTI test during relapse, 1st and 3rd months after relapse were compared in relapsing MS patients. The mean duration of RTI test was significantly shorter during the 1st

month after relapse than during the relapse (p<0,001). Also the mean scores of the most RTI test values were significantly shorter during the 1st month after relapse than during the relapse: the mean score of RTISimot was by 61.23 msec., RTISiret - by 33.37 msec., RTIFichomot - by 68.33 msec. and RTIFichoret - by 30.69 msec. shorter during the 1st month after relapse than during the relapse (p<0.001), however, the mean scores during the 1st and 3rd months after relapse didn't differ (p>0.05). And also as in MS patients and CG the only simple accuracy score didn't differ during the relapse, 1st and 3rd months after relapse (p>0.05) (Table 7).

Table 7. **The mean scores of RTI test during and after MS relapse in relapsing patients**

Test	**MSr1 group (N-60)**	**MSr2 group (N-60)**	**MSr3 group (N-60)**	**ANOVA**	**Post hoc**
RTI duration (sec.)	355.00± 79.46	313.85± 30.78	318.43± 52.07	F=10.06; p<0.001*	MSr1>MSr2,MSr3 MSr2=MSr3
RTIFicho-mot (msec.)	569.30± 182.95	500.97± 135.12	480.69± 170.50	F=12.42; p<0.001*	MSr1>MSr2,MSr3 MSr2= MSr3
RTIFichoret (msec.)	416.73± 99.74	386.04± 74.08	374.66± 64.95	F=19.85; p<0.001*	MSr1>MSr2,ISp3 MSr2= MSr3
RTISacsco	8.75±0.65	8.83±0.49	8.85±0.69	F=0.58; p=0.561	-
RTISimot (msec.)	631.11± 188.40	569.88± 200.08	554.08± 178.08	F=7.20; p=0.001	MSr1>MSr2,MSr3 MSr2= MSr3
RTISiret (msec.)	392.95± 95.46	359.58± 79.62	352.46± 78.79	F=11.42; p<0.001	MSr1>MSr2,MSr3 MSr2= MSr3

MSr1 – relapsing MS patients during relapse, MSr2 – relapsing MS patients during the 1st mth after relapse, MSr3 – relapsing MS patients during the 3rd mth after relapse, RTI – reaction time, RTIFichomot - five-choice movement time of RTI, RTIFichoret – five-choice reaction time of RTI, RTISacsco – simple accuracy score of RTI, RTISimot – simple movement time of RTI, RTISiret – simple reaction time of RTI.
*- Greenhouse-Geisser criterion was used.

In regression models one of the most important predicting factors that had the impact on the RTI test recovery after relapse was the result of RTI test during the relapse – the better recovery of reaction time values was found in the cases of more severe damage during relapse (p<0.05). In contrast to the SDMT test the result of five-choice movement time of RTI test improved more in older persons with lower education (p<0.05). And the result of five-choice reaction time improved more in the persons who has been rehabilated after relapse treatment (p<0.05).

3.1.2.2 The results of One touch stockings of Cambridge test

The mean duration of OTS test was significantly shorter by 412.57±298.65 sec. in CG than in relapsing MS patients ($p<0.05$), while in stable MS patients the duration didn't differ neither from CG, nor from relapsing MS patients ($p>0.05$). The Mean choice to correct (OTSMechco) and Mean latency to correct (OTSMelaco) were signficantly shorter in CG ($p<0.001$), than in MSr and MSs patients, while the results of these values didn't differ significantly in stable and relapsing MS patients ($p>0.05$). The Mean latency to first choice (OTSMelach) and Problems solved on first choice (OTSProfi) also were significantly shorter in CG, than in relapsing MS patients ($p<0.05$), however, the results of these values in stable MS patients didn't differ neither from CG nor from MSr ($p>0.05$). Mean choice to correct of 1, 5 and 6 moves (OTSMechco 1/5/6) were significantly lower and Problems solved on first choice of 1, 5 and 6 moves (OTSProfi1/5/6) were significantly higher in CG than in relapsing MS patients ($p<0.05$), while OTSMechco and OTSProfi of 2, 3 and 4 moves didn't differ in CG, MSr and MSs patients ($p>0.05$) (Table 8).

Table 8. **The mean scores of OTS test in MS patients and control group**

Test	**MSr group (N-60)**	**MSs group (N-30)**	**CG (N-30)**	**ANOVA**	**Post-hoc**
OTS duration (sec.)	1454.50± 611.77	1277.70± 494.05	1041.93± 313.12	F=6.29; p=0.003	CG<MSr**
OTSMechco	1.39± 0.23	1.30± 0.18	1.19± 0.13	F=11.30; p<0.001	CG<MSs,MSr ISr=ISp**
OTSMelaco	49611.77± 26533.25	39380.81± 18612.74	29563.41± 10565.91	F=8.88; p<0.001	CG<MSs,MSr MSs=MSr**
OTSMelach	34015.14± 19905.59	29910.52± 16140.60	23038.46± 8798.53	F=4.26; p=0.016	CG<MSr**
OTSProfi	17.40± 2.95	18.57± 2.54	20.20± 2.33	F=10.79, p<0.001	CG<MSr*
OTSMechco1	1.09± 0.16	1.03± 0.09	1.03± 0.08	F=3.68; p=0.028	CG<MSr**
OTSMechco2	1.12± 0.16	1.11± 0.17	1.04± 0.09	F=3.00; p=0.054	-
OTSMechco3	1.14± 0.21	1.11± 0.14	1.06± 0.11	F=2.27; p=0.107	-
OTSMechco4	1.39± 0.43	1.33± 0.35	1.22± 0.32	F=2.06; p=0.132	-
OTSMechco5	1.55± 0.41	1.48± 0.42	1.33± 0.27	F=3.37; p=0.038	CG<MSr*
OTSMechco6	2.09± 0.78	1.73± 0.50	1.45± 0.36	F=10.67; p<0.001	CG,MSs<MSr, CG=MSs**
OTSProfi1	3.68± 0.50	3.87± 0.35	3.90± 0.31	F=3.37; p=0.038	CG>MSr**

OTSProfi2	3.53± 0.60	3.57± 0.68	3.83± 0.38	F=2.89; p=0.060	-
OTSProfi3	3.52± 0.68	3.60± 0.50	3.77± 0.43	F=1.85; p=0.162	-
OTSProfi4	2.87± 1.11	3.10± 0.92	3.37± 0.89	F=2.47; p=0.089	-
OTSProfi5	2.30± 1.05	2.53± 1.01	2.87± 0.86	F=3.27; p=0.041	CG>MSr*
OTSProfi6	1.47± 1.17	1.90± 1.06	2.50± 1.01	F=8.80; p<0.001	CG>MSr*

MSr – relapsing MS patients, MSs – stable MS patients, CG – control group, OTS – One touch stockings of Cambridge, OTSMechco – Mean choice to correct of OTS, OTSMelaco – Mean latency to correct of OTS, OTSMelach – Mean latency to first choice of OTS, OTSProfi – Problems solved on first choice of OTS, OTSMechco1/2/3/4/5/6 – Mean choice to correct of 1/2/3/4/5/6 moves of OTS, OTSProfi1/2/3/4/5/6 – Problems solved on first choice of 1/2/3/4/5/6 moves of OTS.

* Bonferroni test was used for post-hoc analysis

** Tamhane test was used for post-hoc analysis

The mean duration of OTS and OTSMelaco in relapsing MS patients were significantly shorter during the 1st and 3rd months after relapse than during the relapse ($p<0.001$). OTSMechco was significantly shorter and OTSProfi significantly higher during the 1st month after relapse than during the relapse ($p<0.001$), however, OTSMechco and OTSProfi didn't differ in MSr2 and MSr3 groups ($p>0.05$). On the contrary, OTSMelach didn't differ in MSr1 and MSr2 groups ($p>0.05$), but in MSr3 group it was significantly shorter than in MSr1 and MSr2 groups ($p<0.001$). The differences between OTSMechco and OTSProfi of different moves results were more obvious the more difficult task was – the result of OTSMechco of 3 moves was significantly lower and the result of OTSProfi of 3 moves was significantly higher during the 3rd month after relapse than during relapse, OTSMechco of 4 and 5 moves were significantly lower and OTSProfi of 4 and 5 moves significantly higher during the 1st month after relapse, while OTSMechco of 6 moves was significantly lower and OTSProfi of 6 moves significantly higher during the 1st and during the 3rd months after relapse than during relapse ($p<0.05$) (Table 9).

Table 9. **The mean scores of OTS test during and after MS relapse in relapsing patients**

Test	**MSr1 group (N-60)**	**MSr2 group (N-60)**	**MSr3 group (N-60)**	**ANOVA**	**Post hoc**
OTS duration (sec.)	1454.50± 611.77	1178.33± 455.94	1066.50± 434.74	F=33.33; p<0.001	MSr1>MSr2>MSr3
OTSMechco	1.39± 0.23	1.25±0.16	1.23±0.16	F=38.14; p<0.001*	MSr1>MSr2,MSr3 MSr2=MSr3

OTSMelaco	49611.77± 26533.25	39540.35± 22162.33	33367.05± 18379.60	F=37.98; p<0.001*	MSr1>MSr2>MSr3
OTSMelach	34015.14± 19905.59	30295.95± 18570.48	25626.36± 14638.89	F=14.04; p<0.001*	MSr1,MSr2>MSr3 MSr1=MSr2
OTSProfi	17.40± 2.95	19.22±2.33	19.70±2.37	F=29.90; p<0.001*	MSr1>MSr2,MSr3 MSr2=MSr3
OTSMechco1	1.09± 0.16	1.03±0.86	1.03±0.09	F=5.85; p=0.004*	MSr1>MSr2,MSr3 MSr2=MSr3
OTSMechco2	1.12± 0.16	1.13±0.18	1.10±0.15	F=0.41; p=0.644*	-
OTSMechco3	1.14± 0.21	1.08±0.14	1.07±0.12	F=4.35; p=0.027*	MSr1>MSr3
OTSMechco4	1.39± 0.43	1.18±0.24	1.18±0.31	F=13.50; p<0.001*	MSr1>MSr2,MSr3 MSr2=MSr3
OTSMechco5	1.55± 0.41	1.36±0.32	1.40±0.32	F=6.81; p=0.004*	MSr1>MSr2,MSr3 MSr2=MSr3
OTSMechco6	2.09± 0.78	1.75±0.58	1.60±0.45	F=21.04; p<0.001*	MSr1>MSr2>MSr3
OTSProfi1	3.68± 0.50	3.87±0.34	3.90±0.30	F=5.44; p=0.009*	MSr1<MSr3
OTSProfi2	3.53± 0.60	3.53±0.57	3.60±0.59	F=0.38; p=0.687*	-
OTSProfi3	3.52± 0.68	3.72± 0.45	3.75±0.44	F=4.56; p=0.023*	MSr1<MSr3
OTSProfi4	2.87± 1.11	3.42±0.77	3.53±0.70	F=15.99; p<0.001*	MSr1<MSr2,MSr3 MSr2=MSr3
OTSProfi5	2.30± 1.05	2.75±1.00	2.75±0.93	F=5.32; p=0.01	MSr1<MSr3
OTSProfi6	1.47± 1.17	1.93±1.11	2.13±1.07	F=8.76; p=0.001	MSr1<MSr2,MSr3 MSr2=MSr3

MSr1 – relapsing MS patients during relapse, MSr2 – relapsing MS patients during the 1st mth after relapse, MSr3 – relapsing MS patients during the 3rd mth after relapse, OTS – One touch stockings of Cambridge, OTSMechco – Mean choice to correct of OTS, OTSMelaco – Mean latency to correct of OTS, OTSMelach – Mean latency to first choice of OTS, OTSProfi – Problems solved on first choice of OTS, OTSMechco1/2/3/4/5/6 – Mean choice to correct of 1/2/3/4/5/6 moves of OTS, OTSProfi1/2/3/4/5/6 – Problems solved on first choice of 1/2/3/4/5/6 moves of OTS.
*- Greenhouse-Geisser criterion was used.

Also in the case of OTS test one of the most important predicting factor that had the impact on the OTS test results after relapse was the result of OTS test during the relapse – better recovery was found in more severe cases ($p<0.05$). Also better recovery was found in MS patients with longer duration of the disease and in whom the immunomodulatory therapy was initiated immediately after relapse treatment or it was continued during the relapse and 1st month after relapse ($p<0.05$).

3.1.2.3 The results of Paired Associates Learning test

The mean duration of PAL test was significantly shorter by 194.27 and 101.94 sec. in CG than in relapsing and stable MS patients (p=0.001). Mean errors to success (PALMeer) and Mean trials to success (PALMetr) also were significantly lower in CG, than MSs and MSr patients (p<0.001). First trial memory score (PALfitme) and Stages completed on first trial (PALStfir) were significantly higher in CG, than relapsing MS patients (p<0.05) and in stable MS patients the results didn't differ neither from CG, nor from relapsing MS patients (p>0.05). Total errors (PALToer) and Total trials (PALTotr) of PAL were significantly lower in CG than in MSs and MSr patients (p<0.001). The results of PALToer and PALTotr at different pattern stages were significantly worse and the differences were more greater between all three groups the more difficult task was – at 1, 2 and 3 figures stages there were no significant differences between all three groups (p>0.05), at 6 figures stage MSr patients made significantly more errors and they needed more trials to complete this stage than CG and MSs patients (p<0.05), and at 8 figures stage also MSr and MSs patents made significantly more errors and they needed more trials than CG (p<0.05), while the results in CG and MSs didn't differ (Table 10).

Table 10. **The mean scores of PAL test in MS patients and control group**

Test	**MSr group (N-60)**	**MSs group (N-30)**	**CG (N-30)**	**ANOVA**	**Post-hoc**
PAL duration (sec.)	660.10±281.11	567.77±151.95	465.83±112.85	F=7.92; p=0.001	CG<MSs,MSr MSs=MSr**
PALfitme	18.35±3.38	19.77±3.24	21.23±3.48	F=7.50; p=0.001	CG>MSr*
PALMeer	2.20±1.63	1.61±1.18	0.85±0.76	F=10.20; p<0.001	CG< MSs,MSr MSs=MSr**
PALMetr	1.76±0.46	1.58±0.39	1.35±0.26	F=10.42; p<0.001	CG<MSs,MSr MSs=MSr**
PALStac	8±0	8±0	8±0	-	-
PALStfir	5.58±0.77	5.90±0.96	6.20±1.03	F=5.01; p=0.008	CG>MSr*
PALToer	17.63±13.08	12.70±9.60	6.77±6.06	F=10.15; p<0.001	CG<MSs,MSr, MSs=MSr**
PALToer1	0	0	0	-	-
PALToer2	0.18±0.62	0.23±0.57	0.13±0.51	F=0.22; p=0.803	-
PALToer3	1.17±1.91	0.90±1.40	0.63±1.35	F=1.06; p=0.350	-

PALToer6	5.52±5.04	3.27±4.51	1.77±1.98	F=8.08; p=0.001	CG<MSr**
PALToer8	10.82±8.99	8.47±6.86	4.23±3.64	F=7.79; p=0.001	CG<MSs,MSr MSs=MSr**
PALTotr1	2	2	2	-	-
PALTotr2	2.13±0.39	2.17±0.38	2.07±0.25	F=0.62; p=0.540	-
PALTotr3	2.58±0.93	2.43±0.63	2.33±0.61	F=1.09; p=0.340	-
PALTotr6	3.02±1.44	2.17±1.34	1.80±0.76	F=10.38; p<0.001	CG,MSs<MSr MSs=CG**
PALTotr8	4.32±2.25	3.90±2.07	2.57±1.14	F=7.85; p=0.001	CG<MSs,MSr MSs=MSr**
PALTotr	14.05±3.71	12.67±3.13	10.77±2.11	F=10.39; p<0.001	CG<MSs,MSr MSs=MSr**

MSr – relapsing MS patients, MSs – stable MS patients, CG – control group, PAL - Paired Associates Learning, PALfitme - First trial memory score of PAL, PALMeer - Mean errors to success of PAL, PALMetr - Mean trials to success of PAL, PALStac - Stages completed of PAL, PALStfir - Stages completed on first trial of PAL, PALToer - Total errors of PAL, PALToer1/2/3/6/8 - Total errors at 1, 2, 3, 6 and 8 figures stages of PAL, PALTotr - Total trials of PAL, PALTotr1/2/3/6/8 - Total trials at 1, 2, 3, 6 and 8 figures stages of PAL.

* Bonferroni test was used for post-hoc analysis

** Tamhane test was used for post-hoc analysis

The results of PAL test during relapse, 1st and 3rd months after relapse were compared in relapsing MS patients. PAL duration was significantly longer, PALMeer, PALMetr, PALToer and PALTotr were significantly higher while PALfitme and PALStfir significantly lower during the relapse than during the 1st month after relapse ($p<0.05$) and the results of these values didn't differ during the 3rd and 1st months after relapse in relapsing MS patients ($p>0.05$) (Table 11).

Table 11. **The mean scores of PAL test during and after MS relapse in relapsing patients**

Test	**MSr1 group (N-60)**	**MSr2 group (N-60)**	**MSr3 group (N-60)**	**ANOVA**	**Post hoc**
PAL duration (sec.)	660.10± 281.11	532.48± 139.39	523.93± 152.71	F=18.88; p<0.001*	MSr1>MSr2,MSr3 MSr2=MSr3
PALfitme	18.35±3.38	20.45±3.33	20.80±3.71	F=21.46; p<0.001	MSr1>MSr2,MSr3 MSr2=MSr3
PALMeer	2.20±1.63	1.26±1.04	1.13±1.07	F=35.84; p<0.001*	MSr1>MSr2,MSr3 MSr2=MSr3
PALMetr	1.76±0.46	1.46±0.32	1.42±0.37	F=31.46; p<0.001	MSr1>MSr2,MSr3 MSr2=MSr3
PALStac	8	8	8	-	-
PALStfir	5.58±0.77	6.13±0.91	6.15±1.09	F=12.36; p<0.001	MSr1<MSr2,MSr3 MSr2=MSr3
PALToer	17.63±13.08	10.05±8.28	9.05±8.59	F=35.76;	MSr1>MSr2,MSr3

				p<0.001*	MSr2=MSr3
PALToer1	0	0	0	-	-
PALTotr2	0.18±0.62	0.13±0.47	0.10±0.40	F=0.45; p=0.604*	-
PALToer3	1.17±1.91	0.60±1.21	0.62±1.62	F=3.50; p=0.04*	-
PALToer6	5.52±5.04	2.55±2.91	2.50±3.33	F=17.63; p<0.001*	MSr1>MSr2,MSr3 MSr2=MSr3
PALToer8	10.82±8.99	6.77±6.47	5.83±5.82	F=15.80; p<0.001*	MSr1>MSr2,MSr3 MSr2=MSr3
PALTotr1	2	2	2	-	-
PALTotr2	2.13±0.39	2.08±0.28	2.07±0.25	F=0.81; p=0.447*	-
PALTotr3	2.58±0.93	2.32±0.65	0.62±1.62	F=67.10; p<0.001*	MSr1>MSr3
PALTotr6	3.02±1.44	2.05±1.14	1.93±1.00	F=18.93; p<0.001*	MSr1>MSr2,MSr3 MSr2=MSr3
PALTotr8	4.32±2.25	3.27±1.77	3.03±1.83	F=28.04; p<0.001*	MSr1>MSr2,MSr3 MSr2=MSr3
PALTotr	14.05±3.71	11.72±2.57	11.33±2.88	F=32.57; p<0.001	MSr1>MSr2,MSr3 MSr2=MSr3

MSr1 – relapsing MS patients during relapse, MSr2 – relapsing MS patients during the 1st mth after relapse, MSr3 – relapsing MS patients during the 3rd mth after relapse, PAL - Paired Associates Learning, PALfitme - First trial memory score of PAL, PALMeer - Mean errors to success of PAL, PALMetr - Mean trials to success of PAL, PALStac - Stages completed of PAL, PALStfir - Stages completed on first trial of PAL, PALToer - Total errors of PAL, PALToer1/2/3/6/8 - Total errors at 1, 2, 3, 6 and 8 figures stages of PAL, PALTotr - Total trials of PAL, PALTotr1/2/3/6/8 - Total trials at 1, 2, 3, 6 and 8 figures stages of PAL.
*- Greenhouse-Geisser criterion was used.

Better recovery of PAL test results after MS relapse was found in MS patients with more severe visual memory impairment during relapse, in older patients with longer duration of the disease and treated with methylprednisolone ($p<0.05$).

3.1.2.4 The results of Spatial Working Memory test

The mean duration of SWM test was significantly shorter, Between errors (SWMbeer) and Total errors (SWMtoer) were significantly smaller in CG than in MS patients (relapsing and stable) ($p<0.001$), while the results of these values in MSr and MSs patients didn't differ ($p>0.05$). Between errors for 4 boxes (SWMbeer4) and Total errors for 4 boxes (SWMtoer4) didn't differ in all three groups ($p>0.05$). As in the cases of OTS and PAL, the differences of SWMbeer and SWMtoer for different boxes stages in all three groups were more obvious the more difficult task

was: SWMbeer6 and SWMtoer6 were significantly smaller in CG than in MSr patients ($p<0.001$), while the results of MSs patients didn't differ neither from CG nor from MSr patients ($p>0.05$); SWMbeer8 and SWMtoer8 were significantly lower in CG than in MSs and MSr patients ($p<0.001$), while in MS patients the results didn't differ ($p>0.05$). The Strategy of SWM test was significantly worse in MSr patients than in CG and MSs patients ($p<0.05$) while in those the Strategy didn't differ ($p>0.05$) (Table 12).

Table 12. **The mean scores of SWM test in MS patients and control group**

Test	**MSr group (N-60)**	**MSs group (N-30)**	**CG (N-30)**	**ANOVA**	**Post-hoc**
SWM duration (sec.)	591.87±153.19	538.67±101.45	458.00±95.21	F=10.83; p<0.001	CG<MSs,MSr MSs=MSr**
SWMbeer	31.75±19.67	22.60±18.41	10.73±10.39	F=14.61; p<0.001	CG<MSs,MSr MSs=MSr**
SWMbeer4	1.07±1.91	0.87±1.72	0.23±0.57	F=2.64; p=0.075	-
SWMbeer6	8.22±8.61	4.83±6.08	1.87±2.49	F=8.77; p<0.001	CG<MSr**
SWMbeer8	22.30±12.18	16.90±11.96	8.63±9.06	F=14.36; p<0.001	CG<MSs,MSr MSs=MSr*
SWMstrat	33.95±5.27	32.60±4.17	30.00±4.60	F=6.62; p=0.002	CG,MSs<MSr CG=MSs*
SWMtoer	33.03±19.94	23.40±19.02	11.37±11.08	F=14.85; p<0.001	CG<MSs,MSr MSs=MSr**
SWMtoer4	1.12±1.94	0.90±1.77	0.23±0.57	F=2.86; p=0.061	-
SWMtoer6	8.58±8.60	4.90±6.31	1.93±2.66	F=9.53; p<0.001	CG<MSr**
SWMtoer8	23.18±12.53	17.40±12.35	9.13±9.70	F=14.17; p<0.001	CG<MSs,MSr MSs=MSr*

MSr – relapsing MS patients, MSs – stable MS patients, CG – control group, SWM – Spatial Working Memory, SWMbeer - Between errors of SWM, SWMbeer4/6/8 - Between errors for 4, 6 and 8 boxes of SWM, SWMstrat – Strategy of SWM, SWMtoer - Total errors of SWM, SWMtoer4/6/8 - Total errors for 4, 6 or 8 boxes of SWM.

* Bonferroni test was used for post-hoc analysis

** Tamhane test was used for post-hoc analysis

The duration of SWM test was significantly shorter during the 1st and 3rd months after relapse than during the relapse ($p<0.001$). SWMbeer and SWMtoer were significantly higher in MSr1 than in MSr2 group and in MSr2 - significantly higher than in MSr3 group ($p<0.001$). Although the results of SWMbeer4 and SWMtoer4 were relatively low (ranged from 0.48 up to 1.12 error), however, significant differences also were found – SWMbeer4 and SWMtoer4 were

significantly lower in MSr3 than MSr1 group ($p<0.05$). SWMbeer6 and SWMtoer6 were significantly higher during relapse and 1st month after relapse than during the 3rd month after relapse ($p<0.001$). SWMbeer8 and SWMtoer8 were significantly higher during relapse than during the 1st and 3rd months after relapse ($p<0.001$), while the results during the 1st and 3rd months didn't differ ($p>0.05$) (Table 13).

Table 13. **The mean scores of SWM test during and after MS relapse in relapsing patients**

Test	**MSr1 group (N-60)**	**MSr2 group (N-60)**	**MSr3 group (N-60)**	**ANOVA**	**Post hoc**
SWM duration (sec.)	591.87± 153.19	553.02± 163.81	530.17± 154.92	F=11.60; p<0.001*	MSr1>MSr2,MSr3 MSr2=MSr3
SWMbeer	31.75± 19.67	24.27± 20.66	20.47± 18.42	F=20.17; p<0.001*	MSr1>MSr2>MSr3
SWMbeer4	1.07±1.91	0.77±1.59	0.48±1.24	F=4.48; p=0.018*	MSr1>MSr3
SWMbeer6	8.22±8.61	6.38±7.62	4.80±6.41	F=10.13; p<0.001*	MSr1,MSr2>MSr3 MSr1=MSr2
SWMbeer8	22.30±12.18	17.12±14.38	15.18±12.43	F=12.20; p<0.001*	MSr1>MSr2,MSr3 MSr2=MSr3
SWMstrat	33.95±5.27	32.10±6.21	31.38±5.98	F=14.90; p<0.001	MSr1>MSr2>MSr3
SWMtoer	33.03±19.94	25.37±21.72	21.27±19.00	F=19.45; p<0.001*	MSr1>MSr2>MSr3
SWMtoer4	1.12±1.94	0.97±2.12	0.48±1.24	F=4.30; p=0.018	MSr1>MSr3
SWMtoer6	8.58±8.60	6.90±8.14	4.97±6.50	F=10.22; p<0.001*	MSr1,MSr2>MSr3 MSr1=MSr2
SWMtoer8	23.18±12.53	17.50±15.04	15.82±12.97	F=11.65; p<0.001*	MSr1>MSr2,MSr3 MSr2=MSr3

MSr1 – relapsing MS patients during relapse, MSr2 – relapsing MS patients during the 1st mth after relapse, MSr3 – relapsing MS patients during the 3rd mth after relapse, SWM – Spatial Working Memory, SWMbeer - Between errors of SWM, SWMbeer4/6/8 - Between errors for 4, 6 and 8 boxesof SWM, SWMstrat – Strategy of SWM, SWMtoer - Total errors of SWM, SWMtoer4/6/8 - Total errors for 4, 6 or 8 boxes of SWM.
*- Greenhouse-Geisser criterion was used.

As in the cases of before assessed tests better recovery of SWM test results after MS relapse was found in MS patients with more severe working memory impairment during relapse, in patients with higher education and longer duration of the disease ($p<0.05$).

4 CONCLUSIONS

1. Cognitive functions assessed with Brief International Cognitive Assessment for MS and computerized CANTABeclipse tests in relapsing MS patients were worse than in stable MS patients.
2. Cognitive functions assessed with Brief International Cognitive Assessment for MS and computerized CANTABeclipse tests in MS patients were worse than in healthy controls.
3. Cognitive functions after MS relapse have improved – the most rapid improvement of neurocognitive data has been seen during the first month after relapse, however, the results of several tests have shown that cognitive improvement still are going up to the third month after relapse.
4. Different cognitive and non-cognitive factors had the impact on the recovery of cognitive functions after MS relapse assessed with BICAMS: the recovery of information processing speed depended on the age, level of education and disability, the recovery of visuospatial memory was observed in treated with methylprednisolone and rehabilitated men, who had biologicaly active interferon-beta and verbal learning – in female, who had relatively short relapse duration. The factors that had the impact on the results of the computerized tests were very heterogenous: the improvement of the reaction time depended on the age, level of education and rehabilitation after relapse, spatial planning – on the level of education, duration of the disease and time of the immunomodulatory therapy initiation and visual memory – on the age, duration of the disease and relapse treatment with methylprednisolone.
5. The computerized tests that were chosen for cognitive evaluation during and after MS relapse are appropriate for the assessment of cognitive disability during the relapse – the most accurate tests are those that assess the impairment of spatial working and visual memories and especially the more complex tasks of these tests.

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2. **Giedraitiene N**, Kaubrys G, Kizlaitiene R, Bagdonaite L, Griskevicius L, Valceckiene V, Stoskus M. Therapeutic Plasma Exchange in Multiple Sclerosis Patients with Abolished Interferon-beta Bioavailability. Med Sci Monit 2015; 26;21:1512–1519. doi: 10.12659/MSM.894119. **„ISI Web of Science".**
3. **Giedraitiene N**, Kizlaitiene R, Budrys V, Kaubrys G, Griskevicius L, Valceckiene V, Stoskus M, Griskevicius A, Audzijoniene J. The effect of therapeutic plasma exchange on the bioavailability of interferon-beta in multiple sclerosis patients. A pilot study. Seminars in Neurology 2013; 17(58): 288–296.

PRESENTATIONS

1. **Giedraitiene N**. Multiple sclerosis relapses: cognition during relapse and assessment possibilities. The 8th Baltic Congress of Neurology. 24-26th Sep 2015. Riga, Latvia.
2. **Giedraitiene N**, Kizlaitiene R., Budrys V, Kaubrys G. The effect of therapeutic plasma exchange on the bioavailability of interferon-beta in multiple sclerosis patients. Baltic conference on multiple sclerosis and autoimmune disorders. 4th Apr 2014. Vilnius, Lithuania.

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1. **Giedraitiene N**, Kizlaitiene R, Kaubrys G. Cognitive assessment with BICAMS battery during and after MS relapse. 32nd Congress of ECTRIMS. 14–17th Sep 2016. London, Great Britain.
2. **Giedraitiene N**, Kizlaitiene R, Kaubrys G. The relationship between the BICAMS battery, disease disability, duration and relapse rate in Lithuanian MS patients. The 10th World Congress on Controversies in Neurology (CONY). 17–20th Mar 2016. Lisbon, Portugal.
3. **Giedraitiene N**, Kizlaitiene R, Kaubrys G. Can the Brief International Cognitive Assessment for MS be helpful in detecting of Cognitive changes during MS relapse? Baltic Conference on Multiple Sclerosis and Autoimmune Disorders. 4th Mar 2016. Tallinn, Estonia.

4. Kizlaitiene R, **Giedraitiene N**, Kaubrys G. Cognitive functions during relapse in Multiple Sclerosis. 8th Baltic Congress of Neurology. 24-26th Sep 2015. Riga, Latvia.
5. **Giedraitiene N**, Kizlaitiene R, Budrys V, Kaubrys G, Griskevicius L, Valceckiene V, Stoskus M, Griskevicius A, Audzijoniene J. The effect of therapeutic plasma exchange on the bioavailability of interferon-beta in multiple sclerosis patients. A pilot study. 21st Annual Meeting of the European Charcot Foundation. 28–30th Nov 2013. Baveno, Italy.

SUMMARY IN LITHUANIAN

KOGNITYVINIŲ FUNKCIJŲ VERTINIMAS IŠSĖTINĖS SKLEROZĖS PAŪMĖJIMO IR ATSISTATYMO LAIKOTARPIAIS REMIANTIS *BICAMS* IR KOMPIUTERIZUOTŲ *CANTAB* TESTŲ REZULTATAIS

SANTRUMPOS

BICAMS - tarptautinis trumpasis išsėtine skleroze sergančių ligonių kognityvinių funkcijų vertinimo rinkinys (angl. *Brief International Cognitive Assessment for Multiple Sclerosis*)

BVMT-R – peržiūrėtas trumpasis regimosios erdvinės atminties testas (angl. *Brief Visuospatial Memory Test-Revised*)

CANTAB – Kembridžio neuropsichologinių kompiuterinių testų rinkinys (angl. *Cambridge Neuropsychological Test Automated Battery*)

CNS - centrinė nervų sistema

CVLT-II - Kalifornijos žodžių išmokimo testas, II leidimas (angl. *California verbal learning test II ed.*)

EDSS - išplėstinė negalios vertinimo skalė (angl. *Expanded Disability Status Scale*)

IS – išsėtinė sklerozė

ISp – išsėtinės sklerozės grupė paūmėjimo laikotarpiu

ISr – išsėtinės sklerozės grupė remisijos laikotarpiu

KG – kontrolinė grupė

KF – kognityvinės funkcijos

OTS - vieno prilietimo Kembridžo kojinių planavimo testas (angl. *One touch stockings of Cambridge*)

PAL - porinių asociacijų išmokimo testas (angl. *Paired Associates Learning*)

RTI – reakcijos laiko testas (angl. *Reaction Time*)

SDMT - skaičių simbolių modalumo testas (angl. *Symbol Digit Modalities Test*)

ĮVADAS

Kognityvinės funkcijos (KF) - vienos dažniausiai pažeidžiamų CNS funkcijų sergant IS. Jų pažeidimas neigiamai įtakoja IS ligonių darbingumą, gyvenimo kokybę ir fizinę nepriklausomybę. Neretai KF sutrikimas ligonių gyvenimo kokybę pablogina net labiau, negu fizinė negalia. Kasdienėje neurologo praktikoje, apžiūrint IS sergantį ligonį, KF dažniausiai netiriamos, nes kognityvinių testų taikymas reikalauja papildomo laiko ir išmanymo, o ir didžioji testų dalis nėra adaptuota ir validuota tirti šias funkcijas Lietuvoje. Siekiant diagnozuoti kognityvinių funkcijų sutrikimus, ypač svarbu naudoti jautrius ir kartu paprastai atliekamus testus kognityviniams pokyčiams tirti, nustatyti šių testų diagnostines slenkstines vertes, ateityje vertinant KF progresavimą arba pablogėjimą ligai paūmėjus. Pastaruoju metu pasaulyje yra paplitęs tarptautinis trumpasis kognityvinių funkcijų vertinimo testų rinkinys (angl. *Brief International Cognitive Assessment for Multiple Sclerosis*, BICAMS), kuris rekomenduojamas naudoti greitai ir naudingai kognityvinių sutrikimų diagnostikai sergant IS. Testai yra pakankamai jautrūs ir patikimi identifikuoti kognityvinių sutrikimų turinčių IS ligonių grupes, tačiau iki šiol nėra aišku, ar testai gali būti tinkami kognityviniams sutrikimams diagnozuoti ligai paūmėjus arba ilgalaikei IS ligonių kognityvinės būklės stebėsenai.

Įprastinėje praktikoje IS paūmėjimas diagnozuojamas vertinant neurologinę ligonio būklę pagal išplėstinę negalios vertinimo skalę (EDSS). Ši skalė yra jautri vertinant ligonio sugebėjimą judėti, leidžia kiekybiškai įvertinti ligos progresavimą, tačiau menkai atspindi elgsenos ir pažinimo funkcijas ir ypač jų kitimus ligai paūmėjus arba jai progresuojant. Neabejojama, jog IS paūmėjimo metu KF gali būti pažeidžiamos taip pat dažnai, kaip ir visos kitos fizinės būklės pokyčius sukeliančios sistemos. Netgi manoma, jog sergant IS egzistuoja vadinami izoliuoti kognityviniai paūmėjimai, kurie tikriausiai dėl tinkamų KF vertinimo metodų stokos yra gerokai dažnesni, nei numanoma.

Nepaisant šios temos svarbos, KF pažeidimo reikšmė ir dinamika paūmėjimo metu bei atsistatymo laikotarpiu netyrinėta. Duomenų bazėse randama tik keletas straipsnių, kuriuose aprašomi pavieniai KF kitimų paūmėjimo metu įvertinimo atvejai arba tiesiog retrospektyviai buvo svarstoma apie paūmėjimo įtaką IS ligonių pavienių testų rezultatams, tačiau KF paūmėjimo metu ir atsistatymo laikotarpiu netirtos. Todėl aktyviai diskutuojama dėl reikalingumo atlikti papildomas studijas, kurios vertintų IS ligonių kognityvinę būklę paūmėjimo metu bei aprašytų kliniškai reikšmingus neuropsichologinių testų pokyčius.

Darbo tikslas

Įvertinti išsėtine skleroze sergančiųjų ligonių kognityvines funkcijas ligai paūmėjus, jų dinamiką po paūmėjimo, naudojant trumpąjį kognityvinių funkcijų vertinimo testų rinkinį (angl. *Brief International Cognitive Assessment for Multiple Sclerosis,* BICAMS) ir kompiuterizuotų testų rinkinį CANTABeclipse 3.0.0 (angl. *Cambridge Neuropsychological Test Automated Battery*), bei palyginti rezultatus su sergančiųjų išsėtinės sklerozės ligonių remisijos metu ir kontrolinės grupės asmenų duomenimis.

Darbo uždaviniai

1. Ištirti išsėtine skleroze sergančiųjų ligonių kognityvines funkcijas ligos paūmėjimo laikotarpiu, naudojant trumpąjį kognityvinių funkcijų vertinimo testų rinkinį ir kompiuterizuotus testus bei palyginti duomenis su išsėtine skleroze sergančiųjų remisijos laikotarpiu duomenimis.
2. Palyginti išsėtine skleroze sergančiųjų ligonių kognityvines funkcijas paūmėjimo ir remisijos laikotarpiais su kontrolinės grupės asmenų duomenimis, naudojant trumpąjį kognityvinių funkcijų vertinimo rinkinį ir kompiuterizuotus testus.
3. Įvertinti išsėtine skleroze sergančiųjų ligonių kognityvinių funkcijų dinamiką per tris mėnesius po ligos paūmėjimo.
4. Nustatyti veiksnius, turinčius įtakos kognityvinių funkcijų pokyčiams po ligos paūmėjimo.
5. Išanalizuoti kompiuterizuotais testais įvertintų kognityvinių funkcijų diagnostinę vertę, esant išsėtinės sklerozės paūmėjimui.

Praktinė darbo reikšmė ir naujumas

Pasaulyje labai paplitęs tarptautinis trumpasis kognityvinių funkcijų vertinimo testų rinkinys (BICAMS) buvo išverstas į lietuvių kalbą bei pritaikytas kasdieniam trumpam ir prasmingam IS ligonių kognityvinių funkcijų vertinimui. Naudojant lietuvišką BICAMS variantą bei kompiuterizuotus testus pirmą kartą detaliai įvertintos IS ligonių KF net tik remisijos, bet ir paūmėjimo laikotarpiu, įvertintas šių funkcijų pažeidimo sunkumas. Mūsų tyrimų rezultatai parodė, kad atliekant vien BICAMS testus be didesnių laiko sąnaudų galima būtų įtarti naujai

atsiradusius kognityvinius sutrikimus, o atliekant kompiuterizuotus CANTAB testus šiuos sutrikimus galima patikimai diagnozuoti. Tiek Lietuvos, tiek pasaulio mastu, nebuvo atlikta tokių išsamių IS ligonių grupės tyrimų, kurie įvertintų KF būklę paūmėjimo laikotarpiu bei nustatytų atskirų kognityvinių procesų pokyčių sąsajas su demografinėmis ir klinikinėmis ligonių charakteristikomis, todėl tyrimo rezultatai yra reikšmingi ne tik Lietuvos, bet ir kitų pasaulio šalių mokslininkams ir gydytojams praktikams.

TIRIAMIEJI IR TYRIMO METODIKA

Tyrimas atliktas Vilniaus universiteto Medicinos fakulteto Neurologijos ir neurochirurgijos klinikos Neurologijos centre, Vilniaus universiteto ligoninės Santariškių klinikų Nervų ligų skyriuje ir Konsultacijų poliklinikoje 2012–2016 metais. Tyrime dalyvavo 120 asmenų: 60 ligonių, kuriems nustatytas IS paūmėjimas (ISp), 30 ligonių, kuriems IS buvo remisijos stadijoje (ISr) bei kontrolinę grupę (KG) sudariusių 30 sveikų asmenų. Visiems tiriamiesiems įvertinti demografiniai duomenys (amžius, išsilavinimas, mokymosi trukmė, darbingumas). Sergantiems IS ligoniams įvertintas ligos eigos variantas, fizinė negalia taikant išplėstinę negalios vertinimo skalę (EDSS), ligos trukmė, paūmėjimų skaičius, paūmėjimo buvimas ar nebuvimas, vartojami vaistai bai paūmėjimui skirtas gydymas. Ligoniams, vartojusiems beta interferoną (IFNβ) daugiau nei 1,5 metų, nustatytas IFNβ biologinis aktyvumas.

IS sergantiems ligoniams ir KG asmenims įvertintos kogntyvinės funkcijos naudojant tarptautinį trumpą kognityvinių funkcijų vertinimo testų rinkinį (BICAMS) ir kompiuterizuotą sistemą CANTABeclipse 3.0.0. Tiriamųjų grupei, kuriai nustatytas IS paūmėjimas, kognityvinės funkcijos BICAMS ir CANTAB rinkiniais tirtos ligai paūmėjus, taip pat 1-ą mėn. ir 3-ią mėn. po paūmėjimo.

BICAMS rinkinį sudaro:

1. Skaičių simbolių modalumo testas (SDMT; angl. *Symbol Digit Modalities Test*) - skirtas dėmesio koncentracijai, išlaikymui ir informacijos apdorojimo greičiui nustatyti;
2. Peržiūrėtas trumpasis vizualinės konstrukcinės atminties testas (BVMT-R; angl. *Brief Visuospatial Memory Test-Revised*) - vertina regimąjį erdvinį išmokimą ir atmintį;
3. Kalifornijos žodžių išmokimo testas (CVLT-II; angl. *California verbal learning test II ed.*), II leidimas - vertina žodinį išmokimą ir atmintį.

Iš galimų 22 CANTABeclipse testų į rinkinį buvo įtraukti 4 testai, vertinantys atsako pasirinkimo greitį, erdvinį planavimą, erdvinę darbinę atmintį, epizodinę atmintį, įsiminimą ir darbinės atminties talpą:

1. Reakcijos laiko testas (RTI; angl. *Reaction Time*);
2. Vieno prilietimo Kembridžo kojinių testas (OTS; angl. *One Touch Stockings of Cambridge*);
3. Porinių asociacijų išmokimo testas (PAL; angl. *Paired Associates Learning*);
4. Erdvinės darbinės atminties testas (SWM; angl. *Spatial Working Memory*).

REZULTATAI

KG ir ISr asmenys patikimai nesiskyrė pagal amžių, lytį, išsilavinimo trukmę nuo tiriamosios ISp grupės, o ISp ir ISr grupės taip pat nesiskyrė pagal ligos trukmę, negalios laipsnį, vidutinį paūmėjimų skaičių, remisijos laikotarpį (ISp grupės - laikotarpis iki diagnozuoto paūmėjimo) bei imunomoduliuojančio gydymo trukmę ($p<0,05$). Į galutinę analizę patekusiems asmenims iš viso atlikta 240 testavimų BICAMS ir CANTABeclipse rinkiniais: tiriamoji grupė ISp (N-60) testuota tris kartus, ISr (N-30) ir KG (N-30) – po vieną kartą.

Visų trijų testų – SDMT, BVMT-R ir CVLT-II, bei CVLT-II testo uždelsto prisiminimo, vidutinės rodiklių reikšmės buvo statistiškai patikimai blogesnės IS ligonių (tiek ISp, tiek ISr) nei KG asmenų, o SDMT testo, vertinančio informacijos apdorojimo greitį, ISp ligonių vidutinis balų skaičius buvo patikimai žemesnis nei ISr ligonių ($p<0,001$). Vertinant BICAMS testų rezultatų dinamiką po paūmėjimo, nustatėme, jog visų BICAMS testų bei CVLT-II testo uždelsto prisiminimo vidutiniai balų skaičiai buvo patikimai aukštesni 1-ą mėnesį po paūmėjimo nei paūmėjimo laikotarpiu, o CVLT-II testo rezultatas buvo patikimai aukštesnis ir 3-ią mėn. nei 1-ą po paūmėjimo ($p<0,001$).

Vertinanat veiksnius, turinčius įtakos BICAMS testų rezultatams po paūmėjimo, kiekvienai naujai kognityvinio testo dinamiką aprašančiai reikšmei po paūmėjimo konstruotas tiesinės regresijos modelis, kur nepriklausomais kintamaisiais laikyti įvairūs nekognityvinius simptomus apibūdinančių rodiklių (demografinių, klinikinių ar imunologinių) deriniai. Visuose regresijos modeliuose svarbus BICAMS testų rezultatų pagerėjimui įtaką darantis kintamasis buvo BICAMS testo rezultatas paūmėjimo laikotarpiu – mažesnis balas paūmėjimo laikotarpiu prognozavo geresnį atsistatymą po paūmėjimo. BVMT-R testo pagerėjimui po paūmėjimo

teigiamos įtakos turėjo vyriškoji lytis, o CVLT-II testo – moteriškoji ($p<0,05$). SDMT testo rezultato pagerėjimui lytis įtakos neturėjo, tačiau tai buvo vienintelis testas, kurio rezultato pagerėjimui teigiamos įtakos turėjo jaunesnis tiriamojo amžius ir aukštesnis išsilavinimas, taip pat rezultatas buvo veikiamas EDSS balo paūmėjimo arba remisijos metu bei EDSS balo pokyčių (tarp remisijos ir paūmėjimo) ($p<0,05$). BVMT-R testo rezultato pagerėjimui po paūmėjimo teigiamos įtakos taip pat turėjo paūmėjimui gydyti skirtas metilprednizolonas, biologiškai aktyvus IFN-β bei reabilitacinis gydymas, taikytas po ligos paūmėjimo ($p<0,05$). O CVLT-II testo rezultato pagerėjimui po paūmėjimo teigiamos įtakos turėjo paūmėjimo trukmė – kuo paūmėjimas buvo trumpesnis (arba kuo anksčiau skirtas paūmėjimo gydymas), tuo CVLT-II testo rezultato pagerėjimas po paūmėjimo buvo aukštesnis ($p<0,05$).

RTI testo judėjimo bei reakcijos laiko rodikliai IS ligonių (tiek ISp, tiek ISr grupių) buvo patikimai blogesni nei KG asmenų ($p<0,05$), tačiau ISp ir ISr grupių šie rezultatai patikimai nesiskyrė ($p>0,05$). Šių rodiklių vidutinės reikšmės 1-ą mėnesį po paūmėjimo buvo patikimai trumpesnės, nei paūmėjimo laikotarpiu ($p<0,05$), o 1-ą ir 3-ią mėn. rezultatai nesiskyrė ($p>0,05$). Vertinant veiksnius, turinčius įtakos RTI testo rezultatams po paūmėjimo, svarbus RTI testo rezultato pagerėjimui teigiamą įtaką darantis kintamasis buvo žemesnis RTI testo rezultatas paūmėjimo metu ($p<0.05$). Priešingai nei SDMT testo atveju, penkių pasirinkimų judėjimo laiko rezultato pagerėjimui teigiamos įtakos turėjo vyresnis amžius ir žemesnis išsilavinimas, o penkių pasirinkimų reakcijos laikui – reabilitacinis gydymas po ligos paūmėjimo ($p<0.05$).

OTS testo, vertinančio erdvinį planavimą bei erdvinę darbinę atmintį, rodikliai buvo patikimai blogesni sergančiųjų IS (paūmėjimo ir remisijos laikotarpiu), nei KG asmenų, o testui sudėtingėjant ISp grupės rezultatai buvo patikimai blogesni, nei ISr grupės ($p<0,05$). Po ligos paūmėjimo testo rezultatai buvo patikimai geresni 1-ą mėn., nei paūmėjimo laikotarpiu, o testo užduotims sudėtingėjant rezultatai pagerėjo ne tik 1-ą, bet ir 3-ą mėnesius po ligos paūmėjimo ($p<0,05$). OTS testo rezultatas po paūmėjimo pagerėjo labiau ligonių, kurie turėjo žemesnį OST testo rezultatą paūmėjimo metu, ilgiau sirgo IS bei kuriems imunmoduliuojantis gydymas buvo pradėtas iš karto po paūmėjimo arba jis buvo ir toliau tęsiamas pirmą mėnesį po paūmėjimo ($p<0.05$).

PAL testo, vertinančio regimąją atmintį, rodiklių rezultatai buvo patikimai blogesni KG, nei IS grupės (tiek paūmėjimo, tiek remisijos laikotarpiais). Vertinant PAL testo klaidų ir bandymų skaičiaus rezultatų skirtumus pastebėta, jog testo rezultatai, kaip ir OTS testo atveju, blogėjo

sudėtingėjant užduotims: atliekant lengvas užduotis skirtumų tarp trijų grupių nebuvo ($p>0,05$), atliekant vidutinio sunkumo – ISp grupė testo užduotis atliko patikimai blogiau, nei ISr ir KG ($p<0,05$), o aliekant sunkias užduotis – tiek ISp, tiek ISr grupės užduotis atliko blogiau, nei KG ($p<0,05$). ISp grupės PAL testo rezultatai po ligos paūmėjimo 1-ą mėn. buvo patikimai geresni, nei paūmėjimo laikotarpiu ($p<0,05$), o 1-ą ir 3-ią mėn. po paūmėjimo rezultatai nesiskyrė ($p>0,05$). Vertinant veiksnius, turinčius įtakos PAL testo rezultatams po paūmėjimo, svarbus PAL testo rezultato pagerėjimui teigiamą įtaką darantis kintamasis buvo žemesnis PAL testo rezultatas paūmėjimo metu ($p<0,05$). Taip pat PAL testo rezultato pagerėjimui po paūmėjimo teigiamos įtakos turėjo paūmėjimui gydyti skirtas metilprednizolonas, vyresnis tiriamųjų amžius bei ilgesnė ligos trukmė ($p<0,05$).

SWM testo, vertinančio erdvinę darbinę atmintį, rodiklių rezultatai buvo patikimai blogesni IS sergančiųjų, nei KG ($p<0,05$). Testui sudėtingėjant SWM testo klaidų skaičius didėjo, o skirtumai tarp KG, ISr ir ISp grupių tapo patikimi: atliekant lengvas užduotis skirtumų tarp trijų grupių nebuvo ($p>0,05$), atliekant vidutinio sunkumo – ISp grupė testo užduotis atliko patikimai blogiau, nei ISr ir KG ($p<0,05$), o aliekant sudėtingas užduotis – tiek ISp, tiek ISr grupės atliko blogiau, nei KG ($p<0,05$). Palyginta ISp grupės ligonių SWM testo rezultatų dinamiką po ligos paūmėjimo: klaidų skaičius atliekant lengvas užduotis buvo patikimai didesnis paūmėjimo laikotarpiu, nei 3-ią mėnesį po paūmėjimo, atliekant vidutinio sunkumo užduotis - patikimai didesnis paūmėjimo laikotarpiu ir 1-ą mėnesį po paūmėjimo, nei 3-ią mėn. po paūmėjimo ($p<0,05$), o atliekant sunkias užduotis klaidų skaičius buvo didesnis paūmėjimo laikotarpiu, nei 1-ą mėnesį po paūmėjimo ($p<0,05$), o 1-ą ir 3-ią mėn. po paūmėjimo klaidų skaičius nesiskyrė ($p>0,05$). SWM testo rezultato pagerėjimui po paūmėjimo teigiamos įtakos turėjo ilgesnė mokymosi trukmė bei ilgesnė ligos trukmė ($p<0,05$)

IŠVADOS

1. Kognityvinės funkcijos, tiriamos trumpuoju kognityvinių funkcijų vertinimo testų rinkiniu ir kompiuterizuotais testais, išsėtinės sklerozės paūmėjimo laikotarpiu yra blogesnės nei remisijos laikotarpiu.
2. Kognityvinės funkcijos, tiriamos trumpuoju kognityvinių funkcijų vertinimo testų rinkiniu ir kompiuterizuotais testais, išsėtine skleroze sergančių ligonių yra blogesnės nei sveikų kontrolinės grupės asmenų.

3. Kognityvinės funkcijos po išsėtinės sklerozės paūmėjimo pagerėja – sparčiausias gerėjimas vyksta pirmą mėnesį, o pavienių testų rezultatai rodo, jog kai kurie kognityviniai procesai gali pagerėti per tris mėnesius po ligos paūmėjimo.
4. Sergančių IS ligonių skirtingų kognityvinių funkcijų dinamikai po paūmėjimo įtakos turi skirtingi demografiniai ir klinikiniai veiksniai: informacijos apdorojimo greitį vertinančių testų rezultatų pagerėjimui įtakos turi amžius, išsilavinimas ir negalios laipsnis, regimąją atmintį vertinančių – vyriškoji lytis, gydymas metilprednizolonu, beta interferono aktyvumas ir reabilitacinis gydymas, o žodinį įsiminimą vertinančių – moteriškoji lytis ir paūmėjimo trukmė. Kompiuterizuotų testų dinamikai po ligos paūmėjimo įtakos turintys veiksniai yra labai heterogeniški: reakcijos laiko pagerėjimui įtakos turi amžius, išsilavinimas ir reabilitacinis gydymas po paūmėjimo, erdvinės darbinės atminties – išsilavinimas, ligos trukmė ir IMG pradėjimo laikotarpis, o regimosios atminties – amžius, ligos trukmė ir gydymas metilprednizolonu.
5. Naudoti kompiuterizuoti testai puikiai tinka kognityvinių sutrikimų diagnostikai išsėtinės sklerozės paūmėjimo laikotarpiu – kognityvinių funkcijų sutrikimai tiksliausiai nustatomi testais, vertinančiais erdvinę darbinę bei regimąją atmintis, ypač atliekant sudėtingiausias šių testų užduotis.

PRAKTINĖS REKOMENDACIJOS

1. Nepriklausomai nuo ligos eigos, fazės ar jos trukmės, privalu tirti visų išsėtine skleroze sergančių ligonių kognityvines funkcijas. Ypač svarbu kartotinai vertinti šių funkcijų kitimą, sprendžiant apie jų pablogėjimą paūmėjimo laikotarpiu arba laipsnišką blogėjimą įtariant ligos progresavimą. Efektyviam, greitam ir patikimam kognityvinių funkcijų ištyrimui galima naudoti tarptautinio trumpojo kognityvinių funkcijų vertinimo testų rinkinio (BICAMS) lietuviškąjį variantą.
2. Ligos paūmėjimą reikėtų įtarti atsiradus naujiems, su protine veikla susijusiems ligonio skundams bei objektyviai nustačius atsiradusį naują ir smarkų kognityvinių funkcijų pablogėjimą, bet nesant ryškių fizinės būklės pokyčių.
3. Detalesniam kognityvinių funkcijų ištyrimui paūmėjimo laikotarpiu rekomenduojama naudoti testų rinkinį CANTABeclipse bei labiausiai jautrius kognityvinių sutrikimų ligai paūmėjus testus – OTS testo vidutinį bandymų skaičių iki teisingo atsakymo ir pirmu

bandymu išspręstų užduočių skaičių ties 5 ir 6 ėjimais, PAL testo bendrą klaidų ir bandymų skaičių 6 dėžučių stadijoje, SWM testo strategiją ir bendrą bei tarpinių klaidų skaičių 6 dėžučių stadijoje.

4. Įprastas išsėtinės sklerozės ligonių fizinės negalios stabilizacijos laikotarpis – 1-as mėn. po paūmėjimo, iš dalies gali būti laikomas ir kognityvinių funkcijų stabilizacijos laikotarpiu, tačiau vertėtų nepamiršti, kad kai kurios šių ligonių kognityvinės funkcijos atsistato per 3 mėn. po ligos paūmėjimo, todėl, siekiant nustatyti tikrąją šių funkcijų būklę po paūmėjimo, vertėtų jas ištirti 3-ią mėnesį.
5. Siekiant, kad po paūmėjimo geriau atsitaisytų kognityvinės ir motorinės funkcijos, reikėtų aktyviau svarstyti, ar nereikėtų skirti didesnio metilpredniziolono kiekio paūmėjimui gydyti, po paūmėjimo gydymo svarbu siųsti ligonius reabilitaciniam gydymui, o imunomoduliuojantį gydymą skirti iš karto po paūmėjimo bei tęsti 1-ą mėn. po paūmėjimo.